PATENT
Customer No. 22,852

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Protest of Application of:

Ferenc MARTENYI et al.

Application No.: 10/550,382 (U.S. National Stage of International Application No. PCT/EP2004/003590)

International Filing Date: April 1, 2004

U.S. National Stage entry: September 21, 2005

For: USE OF 10-HYDROXY-10,11-DIHYDROCARBAMAZEPINE DERIVATIVES FOR THE TREATMENT OF AFFECTIVE DISORDERS

Group Art Unit: Unknown

Examiner: Unknown

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PROTEST UNDER 37 C.F.R. § 1.291(a)

Pursuant to 37 C.F.R. § 1.291(a), this paper is submitted in protest of the possible issuance of any U.S. patent which claims priority to or is based on International Application No. PCT/EP2004/003590 ("the '590 application"), which was published by the International Bureau on October 14, 2004, as WO 2004/087168 ("the '168 publication"). *See* Exhibit A.

It is believed that one or more applications for patent claiming priority to or based on the '590 application is pending in the U.S. at the time this Protest is being filed (hereinafter "the pending protested application") because, on information and belief, a national stage application was received in the United States on September 21, 2005, which is based on or claims priority to the '590 application. *See* Exhibit B, which is

correspondence from the U.S. Patent Office confirming entry of the '590 application into the U.S. National Stage.

A Protest may be filed in an application in accordance with 37 C.F.R. § 1.291(b) provided it is "filed prior to the date the application was published under [37 C.F.R.] § 1.211...." Based upon information and research, it is believed that 37 C.F.R. § 1.211 is the rule which governs publication of pending patent applications by the U.S. Patent Office. As such, it is believed that 37 C.F.R. § 1.291(b) allows a Protest to be filed in the U.S. Patent Office during the pendency of a U.S. application as long as it is filed prior to the time the application is published by the U.S. Patent Office.

Although the '590 application was "published" by the International Bureau on October 14, 2004 (see the '168 publication), the Patent Office has interpreted the term "published" (as found, for example, in 37 C.F.R. § 1.211) at 65 Fed. Reg. 57039, stating that "[a]n English language international application designating the United States and published under PCT Article 21(2) is not an application for patent which has been published under 35 U.S.C. § 122(b) (emphasis added)." As such, it is submitted that the '168 publication is not a publication that would prohibit the entry of this paper.

As required by M.P.E.P. § 1901.03, the following statements are believed to be accurate and relevant to the pending protested application, i.e., the '590 application:

(A) Applicants: Ferenc MARTENYI, Markus SCHMUTZ, and Stefanie ZECHNER;

(B) Application No.: 10/550,382 (U.S. National Stage of International Application No. PCT/EP2004/003590)

(C) International Filing Date: April 1, 2004

(D) Title: USE OF 10-HYDROXY-10,11-DIHYDROCARBAMAZEPINE DERIVATIVES FOR THE TREATMENT OF AFFECTIVE DISORDERS

(E) Group Art Unit: Unknown

(F) Examiner: Unknown

(G) Status: U.S. National Stage prosecution entered September 21, 2005.

Furthermore, following reasonable research and inquiry, since the undersigned is unable to ascertain with certainty who the attorney of record or assignee of the pending protested application is, a duplicate copy of this paper is enclosed herewith for the Office to provide to the attorney of record or assignee. The Office is respectfully requested, in accordance with 37 C.F.R. § 1.291(b), to provide a copy of this paper to the attorney of record or assignee as identified in the pending protested application.

In addition, the Office is informed that the present Protest is the first and only Protest filed in the pending protested application on behalf of the Protestor.

Finally, this paper protests the issuance of any claim that claims priority to or is based on the '590 application, to the extent it is directed to the same or substantially the same subject matter as any claim of the '590 application, on the grounds that all the claims of the '590 application are believed to be unpatentable over the references listed in Exhibit C and provided therewith. A concise explanation of the relevance of each listed reference to the claims of the '590 application is set forth below.

I. Standards for Evaluating Anticipation and Obviousness

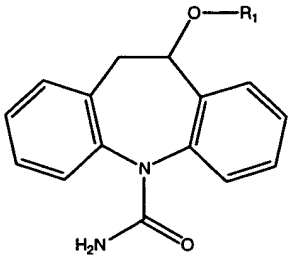
As the Office is aware, in order to anticipate a claim under 35 U.S.C. § 102, a reference must contain all elements of the claim, arranged as in the claim. *See* M.P.E.P. § 2131; *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986). The law requires identity between the claimed invention and the prior art disclosure. *See Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 771, 218 U.S.P.Q. 781, 789 (Fed. 1983). Importantly, inherent disclosure in the prior art of the claimed subject matter anticipates the claim just as express disclosure does. *See, e.g., Schering Corp. v. Geneva Pharm., Inc.,* 339 F.3d 1373, 1379 (Fed. Cir. 2003).

Furthermore, in order to establish a *prima facie* case of obviousness under 35 U.S.C. § 103, three basic criteria must be demonstrated. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. M.P.E.P. § 2143. Second, there must be a reasonable expectation of success. *Id.* Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *Id.*

II. Technical Background

The '590 application is directed to and claims pharmaceutical compositions and treatment of affective disorders with compounds of formula I[1]

[1] Hereinafter, when "formula I" is discussed, it will be in reference to this formula, as disclosed in the '590 application.



(I)

wherein R_1 represents hydrogen or a C_1-C_3 alkyl carbonyl. As discussed in the '590 application, the compound of formula I where R_1 is hydrogen is known. *See* '168 publication at p. 1, citing U.S. Patent No. 3,637,661, issued January 25, 1972. This compound is the monohydroxy derivative of oxcarbazepine ("OXC"), and is referred to as "MHD" for monohydroxy derivative. Dietrich et al., *Oxcarbazepine in Affective and Schizoaffective Disorders*, 34 Pharmacopsychiatry 242 (2001) (hereinafter "Dietrich"); *see also* Exhibit D, figures 1-2. As also discussed in the '590 application, compounds of formula I where R_1 is a C_1-C_3 alkyl carbonyl are also known. *See* '168 publication at p. 1, citing U.S. Patent No. 5,753,646, issued May 19, 1998 ("the '646 patent"). Specifically, the '646 patent discloses the following compounds of formula I wherein R_1 is chosen from C_1-C_3 alkyl carbonyl radicals: 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (acetoxy = C_1 alkyl carbonyl) , 10-propionyl-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (propionyl = C_2 alkyl carbonyl), and 10-butyryloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (butyryloxy = C_3 alkyl carbonyl). *See* the '646 patent at col. 1, lines 64-65 and col. 2, lines 21-24; *see also* Exhibit D, figures 3-5. OXC, MHD, and compounds of formula I wherein R_1 is chosen from C_1-C_3 alkyl carbonyl are all known derivatives of carbamazepine ("CBZ").

A. Compounds of Formula I Wherein R_1 is C_1-C_3 Alkyl Carbonyl

OXC, CBZ, and compounds of formula I wherein R_1 is chosen from C_1-C_3 alkyl carbonyl are known to treat various affective disorders, such as bipolar disorders. *See, e.g.,* Dietrich at p. 243; Keck et al., *Anticonvulsants in the Treatment of Bipolar Disorder*, Journal of Neuropsychiatry, 4:395-405 (1992) (hereinafter "Keck"); and the '646 patent, at col. 3, lines 52-57 and claim 7, respectively.

As shown by these exemplary teachings, the treatment of affective disorders with OXC, CBZ, and compounds of formula I wherein R_1 is chosen from a C_1-C_3 alkyl carbonyl, is well known. As such, the claims of the '590 application directed to the treatment of affective disorders using compounds of formula I wherein R_1 is chosen from a C_1-C_3 alkyl carbonyl (*e.g.,* 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide), and compositions containing these compounds, are unpatentable under 35 U.S.C. § 102.

It is also known that the use of a compound of formula I wherein R_1 is a C_1 alkyl carbonyl (e.g., acetyl), *i.e.*, 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide, is preferable over the use of either CBZ or OXC, due to improved toxicity results. *See* Ambrósio et al., *Neurotoxic/neuroprotective profile of carbamazepine, oxcarbazepine, and two new putative antiepileptic drugs, BIA 2-093 and BIA 2-024*, European Journal of Pharmacology 406:191-201, 199-200 (2000) (hereinafter "Ambrósio"); *see also* Hainzl et al., *Metabolism of two new antiepileptic drugs and their principal metabolites S(+)- and R(-)-10,11-dihydro-10-hydroxy carbamazepine*, 44 Epilepsy Research 197, 205 (2001) (hereinafter "Hainzl"), teaching that 10-acetoxy-

10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide has a preferred metabolism compared to OXC.

In light of the teachings showing a preference for compounds of formula I wherein R_1 is chosen from a C_1 alkyl carbonyl, *i.e.,* 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide, one of skill in the art would have been motivated to substitute 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide for CBZ or OXC in the methods of treating affective disorders described in the various references discussed above, in order to avoid toxicity associated with CBZ and OXC and to obtain an improved metabolism of the compound administered. Since all of these compounds have been shown to be effective in the treatment of affective disorders, the skilled artisan would have had a reasonable expectation of success in the substitution. As such, the claims of the '590 application directed to the treatment of affective disorders using compounds of formula I wherein R_1 is chosen from a C_1-C_3 alkyl carbonyl (*e.g.* 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide), and compositions of these compounds, are likewise unpatentable under 35 U.S.C. § 103.

B. Compounds of Formula I Wherein R_1 is Hydrogen

OXC and compounds of formula I wherein R_1 is chosen from C_1-C_3 alkyl carbonyl are known to metabolize to a compound of formula I wherein R_1 is chosen from hydrogen (*i.e.* MHD). *See* Exhibit E and Hainzl at p. 205; *see also* U.S. Patent Publication No. 20050004102 dated January 6, 2005 (referred to hereinafter as "Schmutz") at [0003]. Furthermore, it is known that the metabolite MHD is the active substance which actually "treats" the relevant condition. *See* Dietrich at p. 243. As is

clearly apparent, one of skill in the art would appreciate that MHD is useful in treating affective disorders. *See, e.g.,* Schmutz at [0004], [0013], and claims.

Further, U.S. Patent No. 6,296,873 to Katzhendler et al. ("the '873 patent"), issued October 2, 2001, at col. 6, lines 21-29 and lines 42-47, and col. 7, lines 1-4, discloses that MHD (as well as OXC and the compounds of formula I wherein R_1 is a C_1-C_3 alkyl carbonyl) can be successfully formulated into a time-release pharmaceutical composition. Schmutz also discloses pharmaceutical compositions comprising MHD. *See, e.g.,* Schmutz at [0020] to [0024] and claims 2-3.

The Federal Circuit has held that when a compound ("prodrug") metabolizes to a metabolite *in vivo*, that *in vivo* metabolism inherently anticipates a later claim to the metabolite. *See, e.g., Schering,* 339 F.3d at 1378-1381 (holding that an earlier patent to a prodrug compound anticipated claims to the metabolite). Similarly, claims which arguably covered methods of treating a condition by administration of a metabolite were construed narrowly to avoid covering such treatment, as the court found that to construe the claims to include such treatment would render them invalid in light of the disclosure and claims in an earlier patent directed to treatment of the same condition with the prodrug compound. *See In re Buspirone Patent Litigation,* 185 F.Supp. 2d 340, 362 (S.D.N.Y. 2002); *see also In re Omeprazole Patent Litigation,* 2001 WL 585534 (S.D.N.Y. 2001) (unreported).

In light of the above, since treatment of affective disorders by a prodrug, such as OXC, which metabolizes to MHD, is known, it logically follows that the treatment of affective disorders with the metabolite MHD is also known. Moreover, as discussed

above, Schmutz expressly discloses and claims treatment of affective disorders by the administration of MHD. As such, the claims of the '590 application directed to the treatment of affective disorders using compounds of formula I wherein R_1 is chosen from hydrogen, *i.e.*, MHD, are unquestionably unpatentable under 35 U.S.C. § 102.

Furthermore, since OXC, CBZ, MHD, and compounds of formula I wherein R_1 is chosen from a C_1-C_3 alkyl carbonyl are all known to be effective in the treatment of affective disorders, and since both OXC and compounds of formula I wherein R_1 is chosen from a C_1-C_3 alkyl carbonyl, such as 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide, metabolize to the same active metabolite which is responsible for the actual treatment of the various affective disorders, *i.e.*, MHD, the skilled artisan would have had a reasonable expectation of success in substituting MHD for, *e.g.,* OXC, in the methods of treating affective disorders described in the several references discussed above.

Finally, since MHD is known to be the active substance which treats the affective disorder, one of skill in the art would have been motivated to formulate a composition comprising MHD according to, for example, the '873 patent, for administration to a patient for treatment of affective disorders, as described in, for example, Dietrich, in place of the OXC, thereby administering the active substance directly and avoiding the metabolizing step. As such, the claims of the '590 application directed to the treatment of affective disorders using compounds of formula I wherein R_1 is chosen from hydrogen, and compositions containing these compounds, are likewise unpatentable under 35 U.S.C. § 103.

III. Claim by Claim Analysis of the '590 Application

Further to the above discussion, the table below sets forth an identification of the teachings in the art that would render each element of each claim of the '590 application, as found in the '168 publication, either anticipated under 35 U.S.C. § 102 or *prima facie* obvious under 35 U.S.C. § 103. It is submitted that all of the prior art references relied on herein, other than the Schmutz reference, are prior art under 35 U.S.C. § 102(b) with respect to any application based on or claiming priority to the '590 application.

The teachings of Schmutz are believed to be prior art under at least 35 U.S.C. § 102(e) to any application based on or claiming priority to the '590 application. Schmutz is based on International Application PCT/EP02/12578, filed on November 11, 2002. *See* Schmutz, front page. As such, the effective U.S. filing date of Schmutz is its international filing date of November 11, 2002. The '590 application was filed on April 1, 2004, claiming priority to U.S. Provisional Application No. 60/459,864, filed April 2, 2003. *See* '168 publication, front page. As such, the effective U.S. filing date of the '590 application is April 2, 2003. Thus, Schmutz has an earlier effective U.S. filing date than the '590 application.

Furthermore, the sole named inventor of the Schmutz reference is Markus Schmutz. *See* Schmutz, front page. The named inventors of the '590 application include Ferenc Martenyi, Markus Schmutz, and Stefanie Zechner. *See* '168 publication, front page. It is well settled that a jointly filed application or patent and an application or patent filed solely by one of the joint inventors are applications filed by different legal

entities. *See Ex Parte Utschig*, 156 U.S.P.Q. 156, 157 (B.P.A.I. 1966). Therefore, in light of the above dates and inventorship information, Schmutz constitutes "an application for patent, published under section 122(b), by another, filed in the United States before the invention by the applicant for patent" and is, therefore, prior art under 35 U.S.C. § 102(e)(1).

Further, the publication of International Application PCT/EP02/12578, upon which Schmutz is based, WO 03/042182 A1 ("the '182 publication"), may also be prior art under 35 U.S.C. § 102(a). The '182 publication was published on May 22, 2003, which falls prior to the April 1, 2004, filing date of the '590 application, and as such, would make the '182 publication available as prior art under 35 U.S.C. § 102(a). Although the Protestor notes that the '590 application claims priority to a U.S. Provisional Application filed on April 2, 2003, which is admittedly prior to the May 27, 2003, publication date of the '182 publication, the Protestor has been unable to obtain a copy of this application to determine whether or not the claims of the '590 application, as they appear in the '168 publication, are supported by the disclosure of the U.S. Provisional Application. To the extent the claims are not supported in the priority application, the '182 publication is prior art under 35 U.S.C. § 102(a).

Finally, it is submitted that claims 13-15 are "use" claims, which may be considered indefinite under 35 U.S.C. § 112, first paragraph, or improper under 35 U.S.C. § 101. *See* M.P.E.P. § 2173.05(q), stating that process claims which do not recite any process steps may be rejected under both 35 U.S.C. §§ 101 and 112, first paragraph.

Claim/Element of '590 Application	Teachings in art
1. A method for the treatment of affective disorders in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a compound of formula I wherein R_1 represents hydrogen or C_1-C_3 alkyl carbonyl.	-the '646 patent at col. 1, lines 64-65 and col. 2, lines 21-24, and in claim 2, teaches compounds of formula I wherein R_1 represents a C_1-C_3 alkyl carbonyl; -the '646 patent at col. 3, lines 52-57 and in claim 7 teaches the use of compounds of formula I wherein R_1 represents a C_1-C_3 alkyl carbonyl for the treatment of, *inter alia,* affective disorders; -Dietrich at pp. 242-243 discloses that OXC is useful in the treatment of affective disorders, and that the active metabolite of OXC is MHD (a compound of formula I wherein R_1 represents hydrogen) which is responsible for the treatment of the affective disorders; -Schmutz at [0004], [0024], and claims 1-4, recites that MHD is useful in the treatment of affective disorders, and at [0020] to [0024] and claims 2-3, recites that MHD can be administered as a pharmaceutical composition for the treatment of affective disorders; -the '873 patent at col. 6, lines 21-29 and lines 42-47 and at col. 7, lines 1-4, discloses that MHD, as well as OXC and the compounds of formula I wherein R_1 is a C_1-C_3 alkyl carbonyl, can be successfully formulated into a time release pharmaceutical composition; In light of these teachings, pharmaceutical compositions containing and methods of treating affective disorders with these compounds is known.
2. The method according to claim 1, which comprises administering to said subject every	-Dietrich at p. 243 discloses dosages of OXC which range from 0.9-1.2 g (900-1200 mg), or up to 2.1 g (2100 mg/day) or

Claim/Element of '590 Application	Teachings in art
20 to 28 hours an amount between about 500 and about 3000 mg of a compound of formula I, wherein R_1 represents hydrogen or C_1-C_3 alkyl carbonyl. 3. The method according to claim 2, wherein every 20 to 28 hours an amount between 750 and 2500 mg of a compound of formula I is administered.	3 g (3000 mg) per day, *i.e.,* approximately every 24 hours; other dosages are also disclosed at pp. 243-244; -as discussed above in Hainzl at p. 205, OXC metabolizes to MHD and thus Dietrich's disclosure of administering these dosages of OXC would be understood to be a disclosure of treating the affective disorders with similar amounts of MHD; In light of the teachings of Ambrósio at pp. 199-200 that 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide is less toxic than, e.g., CBZ or OXC, and Hainzl at p. 205 of preferred metabolism, one of skill in the art would have been motivated to administer the preferred 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (*i.e.*, a compound of formula I wherein R_1 represents C_1 alkyl carbonyl) in similar dosages as disclosed by Dietrich for OXC, with the expectation that similar results would be achieved.
4. The method according to claim 1, 2 or 3, wherein the disorder is selected from severe acute mania and manic episodes of bipolar I disorder.	-Schmutz at [0004] discloses MHD for the treatment of bipolar disorder; -Dietrich at pp. 242-243 discloses the treatment of mania with OXC; -Keck at pp. 400-401 discloses OXC for treatment of acute mania; -Keck at p. 398 discloses CBZ for bipolar disorder; -as discussed above in Hainzl at p. 205, since OXC metabolizes to MHD, one of skill in the art would understand Dietrich and Keck to be disclosures of treating mania with MHD, and thus, it is known to treat these conditions with MHD; For the reasons discussed above, in light

Claim/Element of '590 Application	Teachings in art
	of the teachings of Ambrósio at pp. 199-200 that 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide is less toxic than, e.g., CBZ or OXC, and Hainzl at p. 205 of preferred metabolism, one of skill in the art would have been motivated to substitute 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide for Dietrich's OXC and Keck's OXC and CBZ with a reasonable expectation of success.
5. The method according to claim 4, wherein every 20 to 28 hours an amount between 1500 and 2500 mg of a compound of formula I is administered.	-Dietrich at pp. 242-243 discloses the treatment of mania with OXC; -Dietrich at p. 243 discloses dosages of OXC which range from 0.9-1.2 g (900-1200 mg), or up to 2.1 g (2100 mg/day) or 3 g (3000 mg) per day, *i.e.,* approximately every 24 hours; other dosages are also disclosed at pp. 243-244; As discussed above in Dietrich at pp. 242-243 and Hainzl at p. 205, OXC metabolizes to MHD and thus Dietrich's disclosure of administering these dosages of OXC would be understood to be a disclosure of treating the disorders with similar amounts of MHD, and thus it is known to treat mania with these dosages. In light of the teachings of Ambrósio at pp. 199-200 that 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide is less toxic than, e.g., CBZ or OXC, and Hainzl at p. 205 of preferred metabolism, one of skill in the art would have been motivated to administer the preferred 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide in similar dosages as disclosed by Dietrich for OXC, with the expectation that similar results would be achieved.
6. The method according to claim 1, 2	-Dietrich at pp. 242-243 discloses the

Claim/Element of '590 Application	Teachings in art
or 3, wherein the subject is a patient with a history of rapid cycling, with psychotic features, euphoric mania or dysphoric mania.	treatment of mania with OXC in the recited dosage ranges; -as discussed above in Hainzl at p. 205, since OXC metabolizes to MHD, one of skill in the art would understand Dietrich to be a disclosure of treating mania with MHD with similar dosages, and thus, it is known to treat these conditions at similar dosages with MHD; In light of the teachings of Ambrósio at pp. 199-200 that 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide is less toxic than, e.g., CBZ or OXC, and Hainzl at p. 205 of preferred metabolism, one of skill in the art would have been motivated to substitute 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide for Dietrich's OXC with a reasonable expectation of success.
7. A method for the treatment of manic symptoms in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a compound of formula I wherein R_1 represents hydrogen or C_1-C_3 alkyl carbonyl.	-Dietrich at pp. 242-243 discloses the treatment of mania with OXC, which one of skill in the art would understand would treat the associated symptoms of said mania, *i.e.* the manic symptoms; -as discussed above in Hainzl at p. 205, since OXC metabolizes to MHD, one of skill in the art would understand Dietrich to be a disclosure of treating mania with MHD with similar dosages, and thus, it is known to treat these conditions and associated symptoms with MHD; In light of the teachings of Ambrósio at pp. 199-200 that 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide is less toxic than, e.g., CBZ or OXC, and Hainzl at p. 205 of preferred metabolism, one of skill in the art would have been motivated to substitute 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-

Claim/Element of '590 Application	Teachings in art
	carboxamide for Dietrich's OXC with a reasonable expectation of success.
8. A method for the maintenance treatment of affective disorders in a subject in need of such treatment, which comprises administering to said subject every [sic] a therapeutically effective amount of a compound of formula I wherein R_1 represents hydrogen or C_1-C_3 alkyl carbonyl.	-Dietrich at p. 244 discloses that OXC, when used for prophylactic (*i.e.* maintenance) treatment, decreases the frequency and intensity of manic and depressive episodes, and thus, it is known to use this compound for maintenance treatment of affective disorders; -as discussed above in Hainzl at p. 205, since OXC metabolizes to MHD, one of skill in the art would understand Dietrich to be a disclosure of maintenance treatment of affective disorders with MHD, and thus, it is known to use MHD for maintenance treatment of affective disorders; In light of the teachings of Ambrósio at pp. 199-200 that 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide is less toxic than, e.g., CBZ or OXC, and Hainzl at p. 205 of preferred metabolism, one of skill in the art would have been motivated to substitute 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide for Dietrich's OXC with a reasonable expectation of success.
9. The method according to claim 8, which comprises administering every 20 to 28 hours to said subject an amount between about 600 and about 2500 mg of a compound of formula I, wherein R_1, represents hydrogen or C_1-C_3 alkyl carbonyl. 10. The method according to claim 9, wherein every 20 to 28 hours an amount between 750 and 1250 mg of a compound of formula	-Dietrich at p. 244 discloses that OXC, when used for prophylactic (*i.e.* maintenance) treatment, decreases the frequency and intensity of manic and depressive episodes, and thus, it is known to use this compound for maintenance treatment of affective disorders; -Dietrich at p. 243 discloses dosages of OXC which range from 0.9-1.2 g (900-1200 mg), or up to 2.1 g (2100 mg/day) or 3 g (3000 mg) per day, *i.e.* approximately every 24 hours; other dosages are also disclosed at pp. 243-244;

Claim/Element of '590 Application	Teachings in art
I is administered.	-as discussed above in Hainzl at p. 205, OXC metabolizes to MHD and thus Dietrich's disclosure of administering these dosages of OXC would be understood to be a disclosure of treating the affective disorders with similar amounts of MHD; In light of the teachings of Ambrósio at pp. 199-200 that 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide is less toxic than, e.g., CBZ or OXC, and Hainzl at p. 205 of preferred metabolism, one of skill in the art would have been motivated to administer the preferred 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide in similar dosages as disclosed by Dietrich for OXC, with the expectation that similar results would be achieved.
11. The method according to claim 2, 7, 8 or 9 wherein R_1 represents hydrogen.	-as discussed above, Dietrich discloses the various ranges and treatments; -further, as discussed above, one of skill in the art would appreciate that since the OXC of Dietrich metabolizes to MHD (see Dietrich at pp. 242-243), such disclosures are a teaching of similar ranges of and treatments by MHD; -the '873 patent at col. 6, lines 21-29 and lines 42-47; col. 7, lines 1-4, discloses that MHD, as well as OXC and the compounds of formula I wherein R_1 is a C_1-C_3 alkyl carbonyl, can be successfully formulated into a time release pharmaceutical composition;
12. The method according to claim 1, 2, 7, 8 or 9 wherein R_1 represents acetyl.	-the '646 patent at col. 1, lines 64-65 and claim 2 recites the compound of formula I wherein R_1 represents a C_1 alkyl carbonyl, *i.e.* acetyl; -the '646 patent at col. 3, lines 52-57 and claim 7 recites the use of a compound of

Claim/Element of '590 Application	Teachings in art
	formula I wherein R_1 represents acetyl, for the treatment of, *inter alia,* affective disorders; -as discussed above, Dietrich discloses the various ranges and conditions to be treated; In light of the teachings of Ambrósio at pp. 199-200 that 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide is less toxic than, e.g., CBZ or OXC, and Hainzl at p. 205 of preferred metabolism, one of skill in the art would have been motivated to administer the preferred compound of formula I wherein R_1 represents acetyl (*i.e.*, 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide) in similar dosages and for similar conditions as disclosed by Dietrich for OXC, with the expectation that similar results would be achieved. In light of these teachings, pharmaceutical compositions containing and methods of treating affective disorders with a compound of formula I wherein R_1 represents a C_1 alkyl carbonyl, *i.e.* acetyl, is known.
13. The use of a compound of formula I wherein R_1 represents hydrogen or C_1-C_3 alkyl carbonyl or a pharmaceutically acceptable salt thereof, for the treatment of affective disorders.	-the '646 patent at col. 1, lines 64-65 and col. 2, lines 21-24 and claim 2 recites compounds of formula I wherein R_1 represents a C_1-C_3 alkyl carbonyl; -the '646 patent at col. 3, lines 52-57 and claim 7 recites the use of compounds of formula I wherein R_1 represents a C_1-C_3 alkyl carbonyl for the treatment of, *inter alia,* affective disorders; -Dietrich at pp. 242-243 discloses that OXC is useful in the treatment of affective disorders, and that the active metabolite of OXC is MHD which is responsible for the

Claim/Element of '590 Application	Teachings in art
	treatment of the affective disorders; -Schmutz at [0004], [0024], and claims 1-4, recites that MHD is useful in the treatment of affective disorders, and at [0020] to [0024] and claims 2-3, recites that MHD can be administered as a pharmaceutical composition for the treatment of affective disorders; In light of these teachings, the use of these compounds for the treatment of affective disorders is known.
14. The use of a compound of formula I wherein R_1 represents hydrogen or C_1-C_3 alkyl carbonyl or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment of affective disorders.	-the '646 patent at col. 1, lines 64-65 and col. 2, lines 21-24 and claim 2 recites compounds of formula I wherein R_1 represents a C_1-C_3 alkyl carbonyl; -the '646 patent at col. 3, lines 52-57 and claim 7 recites the use of compounds of formula I wherein R_1 represents a C_1-C_3 alkyl carbonyl for the treatment of, *inter alia,* affective disorders; -Dietrich at pp. 242-243 discloses that OXC is useful in the treatment of affective disorders, and that the active metabolite of OXC is MHD which is responsible for the treatment of the affective disorders; -the '646 patent at col. 3, lines 48-51 teaches a method of making a pharmaceutical composition comprising mixing compounds of formula I wherein R_1 represents a C_1-C_3 alkyl carbonyl with a pharmaceutically acceptable carrier; -Schmutz at [0004], [0024], and claims 1-4, recites that MHD is useful in the treatment of affective disorders, and at [0020] to [0024] and claims 2-3, recites that MHD can be administered as a pharmaceutical composition for the treatment of affective disorders;

Claim/Element of '590 Application	Teachings in art
	-the '873 patent at col. 6, lines 21-29 and lines 42-47; col. 7, lines 1-4, discloses that MHD, as well as OXC and the compounds of formula I wherein R_1 is a C_1-C_3 alkyl carbonyl, can be successfully formulated into a time release pharmaceutical composition; In light of these teachings, pharmaceutical compositions and methods of making them, and methods of treating affective disorders with these compounds is known.
15. The use according to claim 13 wherein R_1 represents acetyl.	-the '646 patent at col. 1, lines 64-65 teaches the compound of formula I wherein R_1 represents a C_1 alkyl carbonyl, *i.e.* acetyl; -the '646 patent at col. 3, lines 52-57 and claim 7 recites the use of a compound of formula I wherein R_1 represents acetyl for the treatment of, *inter alia,* affective disorders; In light of these teachings, pharmaceutical compositions containing and methods of treating affective disorders with a compound of formula I wherein R_1 represents acetyl is known.
16. A pharmaceutical composition which incorporates as active agent a compound of formula I wherein R_1 represents hydrogen or C_1-C_3 alkyl carbonyl or a pharmaceutical acceptable salt thereof, for use in the treatment of affective disorders.	-the '646 patent at col. 1, lines 64-65 and col. 2, lines 21-24, and claim 2, recites compounds of formula I wherein R_1 represents a C_1-C_3 alkyl carbonyl; -the '646 patent at col. 3, lines 52-57 and claim 7 recites the use of compounds of formula I wherein R_1 represents a C_1-C_3 alkyl carbonyl for the treatment of, *inter alia,* affective disorders; -the '646 patent at col. 3, lines 48-51 teaches a method of making a pharmaceutical composition comprising mixing compounds of formula I wherein R_1

Claim/Element of '590 Application	Teachings in art
	represents a C_1-C_3 alkyl carbonyl with a pharmaceutically acceptable carrier, and the use of the compounds for the treatment of affective disorders; -Dietrich at pp. 242-243 discloses that OXC is useful in the treatment of affective disorders, and that the active metabolite of OXC is MHD which is responsible for the treatment of the affective disorders; -Schmutz at [0004], [0024], and claims 1-4 recites that MHD is useful in the treatment of affective disorders, and at [0020] to [0024] and claims 2-3 recites that MHD can be administered as a pharmaceutical composition for the treatment of affective disorders; -the '873 patent at col. 6, lines 21-29 and lines 42-47; col. 7, lines 1-4, discloses that MHD, as well as OXC and the compounds of formula I wherein R_1 is a C_1-C_3 alkyl carbonyl, can be successfully formulated into a time release pharmaceutical composition; In light of these teachings, pharmaceutical compositions containing and methods of treating affective disorders with these compounds is known.
17. A combination comprising (a) a compound of formula I wherein R_1 represents hydrogen or C_1-C_3 alkyl carbonyl, and (b) at least one compound selected from the group consisting of lithium, divalproex, conventional antipsychotics, atypical antipsychotics, lamotrigine and	-Dietrich at p. 245 discloses that OXC can be used in combination with lithium to treat affective disorders, and can be used concurrently with antidepressants and neuroleptics; -the '646 patent at col. 3, lines 48-51 teaches a method of making a pharmaceutical composition comprising mixing compounds of formula I wherein R_1 represents a C_1-C_3 alkyl carbonyl with a pharmaceutically acceptable carrier; -the '873 patent at col. 6, lines 21-29 and

Claim/Element of '590 Application	Teachings in art
antidepressants, in which the active ingredients are present in each case in free form or in the form of a pharmaceutical acceptable salt, and optionally at least one pharmaceutically acceptable carrier.	lines 42-47; col. 7, lines 1-4, discloses that MHD, as well as OXC and the compounds of formula I wherein R_1 is a C_1-C_3 alkyl carbonyl, can be successfully formulated into a time release pharmaceutical composition; -Schmutz at [0022] teaches that MHD can be administered for the treatment of affective disorders, such as bipolar disorders, in combination with other active agents such as, for example, antidepressants and anticonvulsants; -*see, e.g.,* Hopkins, et al., *Treating Bipolar Disorder: Toward the Third Millennium*, XVIII (2) Psych. Times 83 (2001), disclosing that the anticonvulsant divalproex, in combination with lithium or CBZ, is useful for treating bipolar disorder; In light of the teachings of Ambrósio at pp. 199-200 that 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide is less toxic than, e.g., CBZ or OXC, and Hainzl at p. 205 of preferred metabolism, one of skill in the art would have been motivated to administer the preferred compound of formula I wherein R_1 represents a C_1 alkyl carbonyl (*i.e.*, 10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide) in similar combinations as disclosed by Dietrich for OXC, with the expectation that similar results would be achieved. Further, in light of the teachings of Schmutz at [0022] of the combination of MHD with anticonvulsants for treatment of bipolar disorders, and the teaching of Hopkins et al. at 84 ,that the anticonvulsant divalproex is useful for treating bipolar disorders in combination with lithium and CBZ, one of skill in the art would have been motivated to combine these compounds and

Claim/Element of '590 Application	Teachings in art
	administer them for the treatment of affective disorders, such as bipolar disorder, with a reasonable expectation of success.
18. The combination according to claim 17, comprising a compound of formula I, wherein R_1 is hydrogen, and olanzapine.	-Schmutz at [0022] teaches that MHD can be administered for the treatment of affective disorders such as bipolar disorders in combination with other active agents such as, for example, antidepressants; -*see, e.g.,* Gelenberg, et al., *Treating Bipolar Disorder: Toward the Third Millennium*, XVIII (4) Psych. Times (electronic version, 7 pages) (2001), disclosing that olanzapine is useful in the treatment of bipolar disorder and decreases depressive symptoms; In light of the disclosure of Schmutz at [0022], teaching the combination of MHD with other compounds such as antidepressants for the treatment of affective disorders such as bipolar disorder, and the disclosure of Gelenberg et al. that olanzapine is effective in the treatment of bipolar disorders and in decreasing depressive symptoms, one of skill in the art would have been motivated to combine MHD and olanzapine and administer it to a patient for the treatment of affective disorders such as bipolar disorders.
19. The combination according to claim 17, comprising a compound of formula I, wherein R_1 is hydrogen, and a compound selected from lithium or divalproex sodium.	-the '873 patent at col. 6, lines 21-29 and lines 42-47; col. 7, lines 1-4, discloses that MHD, as well as OXC and the compounds of formula I wherein R_1 is a C_1-C_3 alkyl carbonyl, can be successfully formulated in a time release pharmaceutical composition; -Dietrich at p. 245 discloses that OXC

Claim/Element of '590 Application	Teachings in art
	(which will metabolize to MHD: see pp. 242-243) can be used in combination with lithium to treat affective disorders; -*see, e.g.*, Baruzzi et al., *Oxcarbazepine: Pharmacokinetic Interactions and Their Clinical Relevance*, 35 Epilepsia (Supp. 3): S14-S19 (1994) for a disclosure of the combination of OXC (which will metabolize to MHD) and valproate, which is the class to which divalproex sodium belongs; -Schmutz at [0022] teaches that MHD can be administered for the treatment of affective disorders such as bipolar disorders in combination with other active agents such as, for example, anticonvulsants; -*see, e.g.*, Hopkins, et al., *Treating Bipolar Disorder: Toward the Third Millennium*, XVIII (2) Psych. Times 83 (2001), disclosing that the anticonvulsant divalproex, in combination with lithium or CBZ, is useful for treating bipolar disorder; In light of these teachings, pharmaceutical compositions containing and methods of treating affective disorders, such as bipolar disorder, with MHD and lithium and valproate drugs such as divalproex are known. Further, in light of the teachings of Schmutz at [0022] of the combination of MHD with anticonvulsants for treatment of bipolar disorders, and the teaching of Hopkins et al. at p. 84 that the anticonvulsant divalproex is useful for treating bipolar disorders in combination with lithium and CBZ, one of skill in the art would have been motivated to combine these compounds and administer them for the treatment of affective disorders such as bipolar disorder, with a reasonable expectation of success.

Claim/Element of '590 Application	Teachings in art
20. Use of a combination according to any one of claims 17 to 19 for the preparation of a medicament for the treatment of affective disorders.	As explained above, use of any of these combinations is known for the treatment of affective disorders. As also explained above, preparation of a pharmaceutical composition for the treatment of affective disorders is known.
21. A commercial package comprising a combination according to any one of claims 17 to 19 together with instructions for simultaneous, separate or sequential use thereof in the treatment of affective disorders.	The combination is not patentable for the reasons set forth above. Commercial packages with instructions for taking the pharmaceutical composition are well known in the art.

IV. Conclusion

For at least the foregoing reasons, it is respectfully submitted that each of the claims of the '590 application, and any claim based on or claiming priority to the '590 application which is directed to the same or substantially the same subject matter as the claims of the '590 application, are unpatentable.

If there is a fee due in connection with this Protest, please charge the fee to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: November 23, 2005

By: _____
Michelle E. O'Brien
Reg. No. 46,203

Attachments: **Exhibits A-E**